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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,099	03/31/2004	Katalin Varadi	P-279.00	9454

7590 01/31/2006

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,099	VARADI ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-23* is/are pending in the application.

4a) Of the above claim(s) *14-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on January 3, 2006 has been received and entered. Claims 1 and 12 have been amended. Claim 9 has been canceled. No claims have been added. Accordingly, claims 1-8, 10-13, 22 and 23 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-8, 1-13, 22 and 23 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Wöber et al. (US 6,124,110) in view of Hawkins et al. (US 5,625,036), Lawson et al. ("The evaluation of complex-dependent alterations in human Factor VIIa*," J Biol Chem 267(7):4834-4843, 1992), Váradi et al. ("Monitoring the bioavailability of FEIBA with a thrombin generation assay," J Thrombosis and Heamostasis 1:2374-2380, 2003), Chan (US 5,952,198), Hogan et a. (US 6,074,826), Weinstein et al. (US 6,576,422) and Dubrow et al. (US 6,756,019), and further in view of Dou et al. (US 2002/0151582) and CRC (CRC Handbook of Chemistry and Physics 51st Ed., R.C. Weast, ed., The Chemical Rubber Co., Cleveland, 1970, p. B-77). The teachings of Wöber et al., Hawkins et al., Lawson et al., Váradi et al., Chan, Hogan et al., Weinstein et al. and Dubrow et al. were discussed in the previous Office action. The prior art does not disclose specifically that the fluorescently labeled thrombin substrate is

soluble in aqueous solution or that the fluorescently labeled thrombin substrate does not form a precipitate when mixed with $CaCl_2$.

Applicants have amended the claims to recite that the thrombin substrate comprises a fluorescent label and that the composition comprising the thrombin substrate and $CaCl_2$ forms a clear solution when dissolved in an aqueous solution. Applicants assert that their invention is not suggested by the prior art, because the specification discloses that the addition of $CaCl_2$ to a fluorescent substrate leads to the formation of a precipitate (presumably Applicants are referring to what occurred in the prior art). Applicants also assert that a dry, powdered substrate is not a lyophilized substrate, that the substrates of Váradi et al. and Lawson et al. are dried and not lyophilized, and that lyophilization can substantially alter the properties of a starting material. Further, Applicants assert that fluorescent substrates are not soluble in aqueous solution.

In reply, Applicants disclose only one substrate specifically, Z-G-G-R-AMC, which is a fluorescently labeled substrate. Applicants' substrate is the same as that used by Váradi et al. (see p. 2375, middle of the right col.). Váradi et al. do not disclose whether or not their substrate is dried or lyophilized, nor do they disclose what it is dissolved in. They disclose only that a 1 mM solution is made. But if Applicants used the same compound and have found that it is water-soluble and may be lyophilized, this compound had the same properties when used by Váradi et al. Váradi et al. do not teach that this compound is not water-soluble or that it may not be lyophilized. Thus, Applicants findings are not surprising or unexpected in view of Váradi et al. Further, Dou et al. disclose that

Z-G-G-R-AMC is soluble in an assay buffer that is 20 mM Tris-HCl, pH 8.0 (see Example 1, paragraphs 54 and 56). Thus, Dou et al. disclose that Applicants' thrombin substrate is soluble in aqueous solution. Also, because Váradi et al. use the same substrate as Applicants, Váradi et al. use a substrate that may be lyophilized, i.e., a substrate that is not damaged by lyophilization. As discussed in the previous Office action (p. 5 and the top of p. 6), the combination of the teachings of Wöber et al., Hawkins et al., Hogan et al., and Váradi et al. suggest a lyophilized preparation of a mixture comprising a fluorescently labeled thrombin substrate and $CaCl_2$.

Regarding Applicants comment that the addition of $CaCl_2$ to a fluorescent substrate leads to the formation of a precipitate, this comment is based on a sentence in the specification that presumably refers to prior art fluorescently labeled substrates, not to Applicants', as it appears to be Applicants' purpose to avoid aqueous assay mixtures with precipitates. Support for this comment in not found in the cited art, nor have Applicants indicated where in the cited art such support is found. The CRC discloses that the solubility of $CaCl_2$ in water 74.5 g/100 ml at 20°C (see p. B-77). The molecular weight of $CaCl_2$ is 110.99. Thus, $CaCl_2$ is soluble in water up to a concentration of about 6.7 M. As a result, $CaCl_2$ is very soluble in water, particularly when used at concentrations of 15 mM (Váradi et al.), or 5.4 mM (see Wöber et al., cols. 4-5, Thrombin Generation Test, in which 10 μl of a 375 mM $CaCl_2$ solution is added to an assay mixture of 700 μl, about a 1:70 dilution), or 11 mM (see Hawkins et al., Examples 6 and 7, cols. 12-13). One of ordinary skill in the art at the time that the invention was made would

not have expected an aqueous mixture comprising a fluorescently labeled substrate and a low concentration of $CaCl_2$ (5-15 mM) to form a precipitate, because the $CaCl_2$ concentrations used in reagents in assays to measure thrombin generation time are far from the solubility limit. Rather, the skilled artisan would have expected this mixture to be soluble in water.

In view of the foregoing, Applicants have not established that their invention is not obvious, and the rejection of record is maintained.

As noted in the second paragraph of Applicants' remarks, the statement in the previous Office action that claims 1-10 are rejected is incorrect. This sentence should have read that claims 1-13, 22 and 23 are rejected, as indicated on the Office Action Summary (Form PTOL-326). Examiner apologizes for this error.

No claim is allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory

action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner, Art Unit 1653

rk/2006-01-23

Rosanne Kosson

ROBERT A. WAX
PRIMARY EXAMINER